



Rodrigues, J. C. L., Erdei, T., Dastidar, A. G., Szantho, G., Burchell, A. E., Ratcliffe, L. E. K., Hart, E. C., Nightingale, A. K., Paton, J. F. R., Manghat, N. E., & Hamilton, M. C. K. (2018). Left ventricular extracellular volume fraction and atrioventricular interaction in hypertension. *European Radiology*. <https://doi.org/10.1007/s00330-018-5700-z>

Peer reviewed version

License (if available):
Unspecified

Link to published version (if available):
[10.1007/s00330-018-5700-z](https://doi.org/10.1007/s00330-018-5700-z)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Springer at <https://link.springer.com/article/10.1007%2Fs00330-018-5700-z>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Title

Left Ventricular Extracellular Volume Fraction and Atrio-Ventricular Interaction in Hypertension

Abstract

Objectives

Left atrial enlargement (LAE) predicts cardiovascular morbidity and mortality. Impaired LA function also confers poor prognosis. This study aimed to determine whether left ventricular (LV) interstitial fibrosis is associated with LAE and LA impairment in systemic hypertension.

Methods

Following informed written consent, a prospective observational study of 86 hypertensive patients (49 ± 15 years, 53% male, office SBP 168 ± 30 mmHg, office DBP 97 ± 4 mmHg) and 20 normotensive controls (48 ± 13 years, 55% male, office SBP 130 ± 13 mmHg, office DBP 80 ± 11 mmHg) at 1.5T cardiovascular magnetic resonance was conducted. Extracellular volume fraction (ECV) was calculated by T1 mapping. LA volume (LAV) was measured with biplane area-length method. LA reservoir, conduit and pump function were calculated with the phasic volumetric method.

Results

Indexed LAV correlated with indexed LV mass ($R=0.376$, $p<0.0001$) and ECV ($R=0.359$, $p=0.001$). However, ECV was the strongest significant predictor of LAE in multivariate regression analysis (odds ratio [95th confidence interval]: 1.24 [1.04–1.48], $p=0.017$).

Indexed myocardial interstitial volume was associated with significant reductions in LA reservoir ($R=-0.437$, $p<0.0001$) and conduit ($R=-0.316$, $p=0.003$) but not pump ($R=-0.167$, $p=0.125$) function. Multiple linear regression, correcting for age, gender, BMI, BP and diabetes, showed an independent decrease of 3.5% LA total emptying fraction for each 10ml/m² increase in myocardial interstitial volume (standard β coefficient: -3.54, $p=0.002$).

Conclusions

LV **extracellular expansion** is associated with LAE and impaired LA reservoir and conduit function. Future studies should identify if targeting diffuse LV fibrosis is beneficial in reverse remodeling of LA structural and functional pathological abnormalities in hypertension.

Key words

Cardiac Imaging Techniques; Magnetic Resonance Imaging; Hypertension; Fibrosis; Strain

Key points

- Left atrial enlargement (LAE) and impairment are markers of adverse prognosis in systemic hypertension but their pathophysiology is poorly understood.
- Left ventricular extracellular volume fraction was the **strongest** independent multivariate predictor of LAE and was associated with impaired left atrial reservoir and conduit function.

- LV interstitial expansion may play a central role in the pathophysiology of adverse atrio-ventricular interaction in systemic hypertension.

Abbreviations

LA	-	Left atrial
LAE	-	Left atrial enlargement
LVH	-	Left ventricular hypertrophy
LV	-	Left ventricular
CMR	-	Cardiovascular magnetic resonance
SBP	-	Systolic blood pressure
DBP	-	Diastolic blood pressure
SSFP	-	Steady state free precession
LVM	-	Left ventricular mass
LAV	-	Left atrial volume
LAVmin	-	Minimal left atrial volume
LAVpre-A	-	Left atrial volume just prior to left atrial contraction
LAVmax	-	Maximal left atrial volume
EDV	-	End-diastolic volume
ESV	-	End-systolic volume
SV	-	Stroke volume
ROI	-	Region of interest
ECV	-	Extracellular volume fraction
ANOVA	-	Analysis of variance
BMI	-	Body mass index
ESC	-	European Society of Cardiology

Introduction

Left atrial (LA) enlargement (LAE) is common in hypertension[1] and postulated to be compensatory to left ventricular hypertrophy (LVH) associated diastolic dysfunction. However, LAE may develop before LVH in hypertension[2] and LAE is an independent predictor of cardiovascular morbidity and mortality[3].

Atrio-ventricular interaction is important; LA function is intimately related to left ventricular (LV) compliance. As LV compliance falls, LA pump function contributes proportionately more to LV filling[4]. However, as LV compliance falls further, LA pump function declines and the LA reverts to mainly functioning as a passive conduit[5]. In hypertension, LA pump function has been shown to be an independent predictor of adverse cardiac events[6].

However, the pathophysiology of LA dilatation and dysfunction in hypertension remains poorly understood. This assessed atrio-ventricular interaction using multi-parametric cardiovascular magnetic resonance (CMR), to investigate the relationship between LV interstitial expansion, a surrogate for diffuse LV fibrosis, and LA size/function. The hypothesis was that increasing LV interstitial expansion would be associated with LAE and impaired LA function.

Methods

Ethics approval and participants

A prospective, observational study of hypertensive patients from a tertiary hypertension clinic undergoing CMR was performed (February 2013–April 2016). The local research ethics committee confirmed the study conformed to governance arrangements. Subjects provided informed, written consent. Baseline demographic and clinical characteristics were recorded. Average office systolic (SBP) and diastolic blood pressures (DBP) were acquired in accordance with International hypertension guidelines[7]. Exclusion criteria were: atrial fibrillation, concomitant myocardial pathology that may confound LAE (e.g. moderate-severe valvular disease and acquired/inherited cardiomyopathy) and estimated glomerular filtration rate $<30\text{ml/min/1.73m}^2$. Normotensive healthy volunteers acted as controls, but did not receive intravenous gadolinium chelate due to ethics approval constraints.

CMR cine protocol

1.5T CMR was performed (Avanto, Siemens Healthineers). Short-axis steady-state free precession (SSFP) cines with whole LV coverage (8mm slice thickness, no slice gap, temporal resolution 38.1ms, echo time 1.07ms, representative field of view 300mm, image matrix 152x192, in-plane pixel size 1.6x1.6mm) were used to measure LV mass (LVM) and volumes, which were indexed to body surface area (Mosteller formula) as before[8].

LA enlargement and function analysis

LA volume (LAV) was measured by biplane area-length[9](**Figure 1**) as follows:

$$LAV = 0.85 \times A_{4c} \times A_{2c} / L$$

Where:

A4c = LA area on 4-chamber cine at end-systole

A2c = LA area on 2-chamber cine at end-systole

L = shortest LA length on either 4-chamber or 2-chamber at end-systole

LA function was assessed using the phasic-volumetric method[10](**Figure 2**) that measures LAV at 3 phases of the cardiac cycle reliably[6]:

1) Minimal LAV (**LAVmin**) at LV end-diastole at mitral valve closure

2) Just prior to LA contraction (**LAVpre-A**)

3) Maximal LAV (**LAVmax**) at end-systole just prior to mitral valve opening.

LA function was estimated as[10]:

1) LA reservoir function:

LA total emptying fraction = $(LAV_{max} - LAV_{min}) / LAV_{max} \times 100\%$

2) LA conduit function:

LA passive emptying fraction = $(LAV_{max} - LAV_{pre-A}) / LAV_{max} \times 100\%$

3) LA pump function:

LA active emptying = $(LAV_{pre-A} - LAV_{min}) / LAV_{pre-A} \times 100\%$

LA expansion index was defined as previously[11][12][13] as:

$(LAV_{max} - LAV_{min}) / LAV_{min} \times 100\%$

LAE was defined as indexed $LAV_{max} \geq 55\text{ml/m}^2$, which is larger than echocardiographic cut-off values[14] but more appropriate for CMR as it represents 2 standard deviations above the CMR mean of healthy subjects[15][16]. Furthermore, a recent publication of 804 normal volunteers confirmed indexed $LAV_{max} 55\text{ml/m}^2$ as the upper limit of normal for men and women[17].

LV volume, mass and functional analysis

A validated and highly reproducible[18] threshold-detection software (CMR42, Circle Cardiovascular Imaging Inc.) was used to include papillary muscles and LV trabeculae in LVM estimation and then include them in blood-pool volume for end-diastolic (EDV),

end-systolic (ESV) and stroke (SV) volume measurements as before[8]. CMR analysis was performed blinded to all other data.

CMR T1-mapping protocol and analysis

Myocardial T1-mapping was performed using a modified look-locker inversion recovery sequence with native and post-contrast sequences dependent upon heart rate at acquisition (**Table 1**). Constant scan parameters were: flip angle 35°, GRAPPA acceleration factor 2, bandwidth 1085 Hz/Px, number of inversions 2, starting TI 120ms, TI increment 80ms. Regions of interest (ROI) were drawn within mid-septum on short-axis, motion-corrected, native T1-maps and copied onto corresponding 15 minutes post-contrast maps, adjusting for partial-voluming and/or artifact, as previously described[19]. Argus software (Siemens, Germany) was used for T1 analysis, as previously described[19]. Extracellular volume fraction (ECV) was calculated using an established formula[19]:

$$ECV = (\Delta R1_{\text{myocardium}} / \Delta R1_{\text{blood-pool}}) \times (1 - \text{haematocrit})$$

Where:

$$\Delta R1 = (1/\text{post-contrast T1} - 1/\text{native T1}).$$

Haematocrit measured from peripheral venous blood sample.

Indexed interstitial volume was calculated by multiplying the ECV by indexed myocardial volume (indexed LVM divided by myocardial specific gravity 1.05g/ml).

Myocardial cell volume fraction was defined, as previously[20], as (1–ECV), and multiplied by indexed LV myocardial volume to generate an estimation of indexed

myocardial cell volume. Excellent reproducibility was demonstrated in a subset of 50 subjects (native T1-mapping intra-class correlation coefficient (ICC): 0.968 (95th confidence interval: 0.951–0.984) and ECV ICC: 0.988 (95th confidence interval: 0.979–0.993)).

CMR strain imaging

Strain imaging was performed offline by software (Tissue Tracking, CMR42, Circle Cardiovascular Imaging Inc.) that tracks myocardial voxels through the cardiac cycle in 2D, based on a previously described algorithm[21][22]. Briefly, the endocardial and epicardial borders (excluding papillary muscles and trabeculae) and the mitral valve annular plane at end-diastole were defined on LV 4-chamber, LV 2-chamber and whole LV short-axis SSFP cine images. Circumferential strain and strain rates were calculated from mean values of mid LV myocardial segments from the short-axis 2-dimensional strain model. Strain analysis was performed blinded to all other data.

Statistical analysis

Statistical analysis was performed in SPSS (v.21, IBM Corp). A power calculation could not be performed for this exploratory observational study because there are no previous studies assessing the atrio-ventricular interaction using non-invasive measures of LV diffuse interstitial fibrosis and LA phasic volume function using any cardiac imaging modality. Normally distributed continuous variables were expressed as mean \pm standard deviation and compared using analysis of variance (ANOVA) with Bonferroni post-hoc correction. Categorical variables were expressed as percentages and interrogated with Chi-square tests. Correlations were assessed with Pearson's

coefficient. General linear models were used to correct for differences in baseline covariates of age, gender, body mass index (BMI), diabetes, office SBP, office DBP and number of anti-hypertensive medications between cohorts. Multiple linear regression was performed to quantify independent impact of indexed interstitial and myocardial cell volumes on indexed LAVmax, LAVmin and LA total emptying fraction, accounting for covariates. Univariate logistic regression identified predictors of LAE and significant univariate variables were tested in a multivariate model to determine independent associations. $P < 0.05$.

Results

Participant demographics

116 hypertensive patients were assessed for eligibility. 30 patients were excluded(**Figure 3**), with final sample size of 86 (49 ± 15 years, 53% male, office SBP 168 ± 30 mmHg, office DBP 97 ± 4 mmHg). 20 normotensive control subjects were recruited (48 ± 13 years, 55% male, office SBP 130 ± 13 mmHg, office DBP 80 ± 11 mmHg). Hypertensive and normotensive subjects were age- and sex-matched(**Table 2**). LAE was present in 27% ($n=23$).

LA size and LV mass

Indexed LVM correlated with indexed LAVmax ($R=0.376$, $P<0.0001$)(**Figure 4A**) and with indexed LAVmin ($R=0.616$, $P<0.0001$)(**Figure 4B**).

Hypertensive subjects with LAE had higher: 1) indexed LVM mass (97 ± 33 g/m² vs 84 ± 22 g/m², $P=0.044$), 2) indexed EDV (89 ± 17 ml/m² vs 73 ± 16 ml/m², $P<0.0001$) and 3) indexed ESV (34 ± 17 ml/m² vs 24 ± 10 ml/m², $P<0.0001$) compared to hypertensive subjects without LAE(**Table 3**), which persisted after correcting for covariates(**Table 4**).

LA size, LV fibrosis and LV strain

There was a positive correlation between ECV and 1) indexed LAVmax ($R=0.359$, $P=0.001$)(**Figure 4C**) and 2) indexed LAVmin ($R=0.390$, $P<0.0001$)(**Figure 4D**).

Hypertensives with LAE had higher ECV ($30\pm4\%$ vs $27\pm3\%$, $P=0.003$)(**Table 2**) and larger indexed LV interstitial volume (28 ± 12 ml/m² vs 21 ± 7 ml/m², $P=0.043$) than hypertensives without LAE(**Table 3**), which persisted after correcting for covariates

(**Table 4**). However, there was no significant difference in indexed LV myocardial cell volume between hypertensive subjects with LAE and those without LAE ($64 \pm 21 \text{ ml/m}^2$ vs $57 \pm 15 \text{ ml/m}^2$, $P=0.106$)(**Table 3**).

Accounting for the covariates of age, gender, BMI, diabetes, office SBP and office DBP, each 10 ml/m^2 increase in indexed LV interstitial volume, a significant independent increase in 1) indexed LAVmax of 4.9 ml/m^2 (standard β coefficient: 4.88, $P<0.0001$) and 2) indexed LAVmin of 5.6 ml/m^2 occurs (standard β coefficient: 5.61, $P<0.0001$). In a separate model, each 10 ml/m^2 increase in indexed LV myocardial cell volume, was also associated with a significant independent increase in 1) indexed LAVmax of 3.2 ml/m^2 (standard β coefficient: 3.20, $P<0.0001$) and 2) indexed LAVmin of 4.7 ml/m^2 (standard β coefficient: 4.74, $P<0.0001$).

Indexed interstitial volume correlated with peak circumferential strain ($R=0.454$, $p<0.0001$), peak systolic strain rate ($R=0.342$, $p=0.001$) and peak diastolic strain rate ($R=-0.380$, $p<0.0001$). Indexed myocardial cell volume also correlated with peak circumferential strain ($R=0.509$, $p<0.0001$), systolic strain rate ($R=0.267$, $p=0.013$) and diastolic strain rate ($R=-0.501$, $p<0.0001$). In turn, indexed LAVmin correlated with peak circumferential strain ($R=0.275$, $p=0.01$), systolic strain rate ($R=0.438$, $p<0.0001$) and diastolic strain rate ($R=-0.273$, $p=0.011$). However, LAVmax only correlated with systolic strain rate ($R=0.405$, $p<0.0001$) and not with peak circumferential strain ($R=0.067$, $p=0.537$) or diastolic strain rate ($R=-0.136$, $p=0.212$).

Predictors of LAE

Indexed LVM, ECV and peak circumferential strain rate were significant predictors of LAE in univariate logistic regression(**Table 5**). ECV and peak circumferential strain rate remained significant predictors in the multivariate model and ECV was the strongest predictor (**Table 5**).

LA function and LV fibrosis

Indexed LV interstitial volume inversely correlated with LA total reservoir function ($R=-0.437$, $P<0.0001$)(**Figure 5A**). Likewise, indexed LV interstitial volume inversely correlated with LA passive conduit function ($R=-0.316$, $P=0.003$)(**Figure 5B**). However, there was no significant correlation between indexed LV interstitial volume and LA pump function ($R=-0.167$, $P=0.125$)(**Figure 5C**). There was a significant decrease in LA expansion index with increasing interstitial volume ($R=-0.377$, $P<0.0001$)(**Figure 5D**).

Accounting for the covariates of age, gender, BMI, diabetes, office SBP and office DBP, each 10ml/m² increase in indexed LV interstitial volume, a significant independent decrease in LA total reservoir function of 3.5% occurs (standard β coefficient: -3.54, $P=0.002$). In a separate model, each 10ml/m² increase in indexed LV myocardial cell volume, was associated a significant independent decrease in LA total reservoir function of 3.2% (standard β coefficient: -3.20, $P=0.006$).

Discussion

We demonstrate the relationship between LV interstitial expansion and LA structure and function in hypertension using CMR. Previous studies have investigated using with T1 mapping techniques in hypertensive patients[23][24][25][26][27], but all have focused exclusively on the LV, with no focus on atrio-ventricular interaction, which has been addressed in the current study. Our novel findings are: 1) increasing LV interstitial volume is associated with increasing LAVmax and LAVmin. 2) increasing LV interstitial volume is also associated with impaired circumferential systolic and diastolic strain rate that are in turn correlate with LAVmin, 3) Increasing LV ECV was the **strongest** independent multivariate predictor of LAE, and 4) LV interstitial fibrotic burden significantly inversely correlates with LA total reservoir function and in LA passive conduit function but not with LA active pump function.

Atrio-ventricular interaction

Hypertensive LV changes are intimately related to LA dynamics. A recent echocardiographic study showed that LV systolic and diastolic dysfunction were associated with increased LAV and LA diastolic stiffness, even in asymptomatic patients[28]. Our study provides further insight at the LV myocardial intra/extracellular level. Although both increases in indexed myocardial cell volume and indexed interstitial volume were independently associated with LAE, the regression coefficient was larger for indexed interstitial volume. Furthermore, ECV was the only independent predictor of LAE in multivariate regression analysis.

Potential for LA reverse remodeling.

We demonstrated no significant relationship between LA pump function and indexed LV interstitial volume. This may suggest a greater LV fibrotic burden is required to cause LA pump dysfunction than is required to cause LA conduit or reservoir dysfunction. A prior CMR study in 210 hypertensive subjects[6] support this notion where, during a median 19 month follow-up, contractile atrial dysfunction was an independent predictor of major adverse clinical events(MACE)[6].

Furthermore, preservation of the proportion of LA contraction to total LV diastolic filling was strongly associated with lower MACE[6]. Decreased LA contractile function may identify those with the most LV diastolic dysfunction and conceivably these are the patients with the most diffuse LV fibrosis. It is therefore possible that failure of LA pump function heralds near end-stage hypertensive cardiac end-organ damage, accounting for the correlation of this imaging biomarker with mortality[6]. Therefore, therapeutic targeting of diffuse LV myocardial fibrosis prior to the onset of overt LA contractile dysfunction may offer the best chance of achieving LA reverse remodeling. Treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers have been associated with LA reverse remodeling in both the spontaneously hypertensive rat[29] and in hypertensive humans[30]. The putative mechanisms by which these agents result in LA reverse remodeling are incompletely understood, potentially include downstream effects of BP reduction or improved LV diastolic function. However, direct suppression of the renin-angiotensin-aldosterone system is also implicated. Our results, showing a correlation between LV fibrosis and LA volume, may offer further pathophysiological insights. Such agents have been demonstrated to result in regression of LV fibrosis in murine models of hypertension[31], which could be a common driver of the LV

diastolic functional improvement and improvement in LA function and structure.

Although not assessed in the current study, it is possible that these drugs cause direct regression of LA fibrosis, having been associated with a reduction in the percentage of fibrosis of LA tissue in spontaneously hypertensive rats treated with Olmesartan compared to controls[29].

Clinical implications

The clinical prognostic importance of LAV independent to LV diastolic dysfunction is debated. In a study of 1,160 elderly patients with cardiovascular disease referred for routine clinical echocardiography, both LV diastolic dysfunction and indexed LAVmax were independent predictors of cardiovascular events[32]. In a younger cohort of 484 subjects in sinus rhythm referred for echocardiography, an elevated indexed LAVmax was the only independent predictor of cardiovascular death and events, and indices of LV diastolic dysfunction were not[33]. Many previous studies have focused on LAVmax but in a study of 41 patients undergoing invasive pressure measurements via left heart cardiac catheterization and CMR on the same day, increased LAVmin had the best ability to predict elevated LV end-diastolic filling pressure[34].

Furthermore, a prior echocardiographic study showed that LAVmin significantly increased with worsening LV diastolic dysfunction and in multivariate models, increasing LAVmin was independently associated with decreasing echocardiographic indices of LV diastolic function, but LAVmax was not[35]. Our study helps explain this by demonstrating a statistically stronger correlation between ECV and indexed LAVmin, than with LAVmax. We also found significant correlation between peak circumferential strain, peak circumferential systolic strain rate and peak

circumferential diastolic strain rate and indexed LAVmin. These findings support the notion that diffuse LV fibrosis is associated with LV diastolic dysfunction, elevated LV end-diastolic filling pressure and in turn LAVmax and LAVmin dilatation. However, whether the fibrotic process starts in the LV and that drives the LA changes, or whether the same fibrotic process occurs simultaneous in the LV and LA remains unanswered.

LA function is also of prognostic importance. In the Dallas Heart CMR study of 1,802 subjects, decreasing LAEF, defined as $(LAV_{max} - LAV_{min})/LAV_{max} \times 100$, was independently associated with mortality[36]. We show a correlation between declining total LA emptying fraction and diffuse LV fibrosis. Furthermore, we demonstrate a significant decrease in LA expansion index, a parameter that predicts LV filling pressure[12], severe LV diastolic dysfunction[13] and all-cause mortality[11], with increasing LV interstitial volume.

Our study highlights the central pathophysiological role of LV diffuse myocardial fibrosis in hypertension. The LV fibrotic burden has associations with structural and functional changes beyond the LV. This suggests that targeting LV fibrosis should be a key therapeutic target but effective anti-fibrotic treatments have proven to be an elusive until very recently. New insights into both the understanding of the development of myocardial fibrosis and novel ways in which to abrogate this process, such as inhibition of interleukin-11[37], at least in animal models, offers hope that the effective therapies for blocking/reversing myocardial fibrosis may be

on the horizon, which may improve LV and LA structure and function in hypertension.

Study limitations

The study was performed in a specialist hypertension clinic population. Further study is required in a larger, more diverse population to enable further analyses such as impact of duration of hypertension and anti-hypertensive regimens on LV diffuse myocardial fibrosis and LA structure/function.

T1 values were recorded in mid-septum owing to lower intra-observer, inter-observer and inter-study variability previously reported in the lateral wall, likely related to a number of confounders, e.g. magnetic susceptibility artifact, receiver coil sensitivity and distance from the receiver coil elements[38]. Nevertheless, more comprehensive segmental T1 quantification has been described[39], but not performed in the current study. Hypertensive remodeling may begin in the septum[40] and therefore only measuring T1 relaxation values here could theoretically result in a overestimation of the degree of interstitial expansion.

LA conduit function was defined as passive emptying fraction. This is an index of one component of conduit function as it only describes the flow that results from change in LA volume during this time interval rather than the entire flow from the pulmonary veins through the LA into the LV during that phase of diastole.

Contemporaneous comprehensive echocardiographic assessment was not available in all study subjects. CMR strain rates have been provided but may be limited by inferior temporal resolution of CMR to echocardiography. Future work could investigate whether diffuse LV myocardial fibrosis is the underlying pathophysiological abnormality, which independently causes both LV diastolic dysfunction and LA dilatation and dysfunction.

LA replacement fibrosis assessment, with LGE or T1 mapping, was not investigated, but may be potentially important[41].

Conclusion

In hypertension, increasing LV interstitial fibrosis is associated with LAE and impaired LA function. ECV was the **strongest** significant independent predictor of LAE in multivariate analysis, and increasing indexed LV interstitial volume significantly and independently resulted in worsening LA reservoir function. Diffuse LV fibrosis may represent a key therapeutic target for reverse remodeling of both LA and LV structural and functional abnormalities in hypertension.

Acknowledgments

This work was supported by the Bristol NIHR Cardiovascular Biomedical Research Unit at the Bristol Heart Institute. The views expressed are those of the authors and not necessarily those of the National Health Service, National Institute for Health Research, or Department of Health. We thank Christopher Lawton, Superintendent Radiographer, and the Bristol Heart Institute CMR radiographers for their expertise

in performing the CMRs. JCLR: Clinical Society of Bath Postgraduate Research Bursary 2014 and Royal College of Radiologists Kodak Research Scholarship 2014. ECH and JFRP are funded by the British Heart Foundation.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

1. Cuspidi C, Rescaldani M, Sala C (2013) Prevalence of echocardiographic left-atrial enlargement in hypertension: a systematic review of recent clinical studies. *Am J Hypertens* 26:456–64. doi: 10.1093/ajh/hpt001
2. Shigematsu Y, Norimatsu S, Ogimoto A et al (2009) The influence of insulin resistance and obesity on left atrial size in Japanese hypertensive patients. *Hypertens Res* 32:500–4. doi: 10.1038/hr.2009.41
3. Modena MG, Muia N, Sgura FA et al (1997) Left atrial size is the major predictor of cardiac death and overall clinical outcome in patients with dilated cardiomyopathy: a long-term follow-up study. *Clin Cardiol* 20:553–60.
4. Appleton CP, Hatle LK, Popp RL (1988) Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 12:426–40.
5. Prioli A, Marino P, Lanzoni L, Zardini P (1998) Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. *Am J Cardiol* 82:756–61.
6. Kaminski M, Steel K, Jerosch-Herold M et al (2011) Strong cardiovascular prognostic implication of quantitative left atrial contractile function assessed by cardiac magnetic resonance imaging in patients with chronic hypertension. *J Cardiovasc Magn Reson* 13:42. doi: 10.1186/1532-429X-13-42
7. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of

- the European Society of Cardiology (ESC). *Eur Heart J* 34:2159–219. doi: 10.1093/eurheartj/eh151
8. Maceira A, Prasad S, Khan M, Pennell D (2006) Normalized Left Ventricular Systolic and Diastolic Function by Steady State Free Precession Cardiovascular Magnetic Resonance. *J Cardiovasc Magn Reson* 8:417–426. doi: 10.1080/10976640600572889
 9. Sievers B, Kirchberg S, Addo M et al (2004) Assessment of left atrial volumes in sinus rhythm and atrial fibrillation using the biplane area-length method and cardiovascular magnetic resonance imaging with TrueFISP. *J Cardiovasc Magn Reson* 6:855–63.
 10. Blume GG, Mcleod CJ, Barnes ME et al (2011) Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr* 12:421–430. doi: 10.1093/ejechocard/jeq175
 11. Hsiao SH, Chiou KR (2013) Left atrial expansion index predicts all-cause mortality and heart failure admissions in dyspnoea. *Eur J Heart Fail* 15:1245–1252. doi: 10.1093/eurjhf/hft087
 12. Hsiao SH, Chu KA, Wu CJ, Chiou KR (2016) Left Atrial Expansion Index Predicts Left Ventricular Filling Pressure and Adverse Events in Acute Heart Failure With Severe Left Ventricular Dysfunction. *J Card Fail* 22:272–9. doi: 10.1016/j.cardfail.2016.01.009
 13. Hsiao SH, Chiou KR (2016) Diastolic Heart Failure Predicted by Left Atrial Expansion Index in Patients with Severe Diastolic Dysfunction. *PLoS One* 11:e0162599. doi: 10.1371/journal.pone.0162599
 14. Paulus WJ, Tschöpe C, Sanderson JE et al (2007) How to diagnose diastolic

- heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 28:2539–50. doi: 10.1093/eurheartj/ehm037
15. Järvinen VM, Kupari MM, Hekali PE, Poutanen VP (1994) Right atrial MR imaging studies of cadaveric atrial casts and comparison with right and left atrial volumes and function in healthy subjects. *Radiology* 191:137–42. doi: 10.1148/radiology.191.1.8134560
 16. Tseng WYI, Liao TY, Wang JL (2002) Normal systolic and diastolic functions of the left ventricle and left atrium by cine magnetic resonance imaging. *J Cardiovasc Magn Reson* 4:443–57.
 17. Petersen SE, Aung N, Sanghvi MM et al (2017) Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *J Cardiovasc Magn Reson* 19:18. doi: 10.1186/s12968-017-0327-9
 18. Childs H, Ma L, Ma M et al (2011) Comparison of long and short axis quantification of left ventricular volume parameters by cardiovascular magnetic resonance, with ex-vivo validation. *J Cardiovasc Magn Reson* 13:40. doi: 10.1186/1532-429X-13-40
 19. Pica S, Sado DM, Maestrini V et al (2014) Reproducibility of native myocardial T1 mapping in the assessment of Fabry disease and its role in early detection of cardiac involvement by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 16:99. doi: 10.1186/s12968-014-0099-4
 20. Flett AS, Sado DM, Quarta G et al (2012) Diffuse myocardial fibrosis in severe

- aortic stenosis: an equilibrium contrast cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging* 13:819–26. doi: 10.1093/ehjci/jes102
21. Bistoquet A, Oshinski J, Skrinjar O (2007) Left ventricular deformation recovery from cine MRI using an incompressible model. *IEEE Trans Med Imaging* 26:1136–53. doi: 10.1109/TMI.2007.903693
 22. Bistoquet A, Oshinski J, Skrinjar O (2008) Myocardial deformation recovery from cine MRI using a nearly incompressible biventricular model. *Med Image Anal* 12:69–85. doi: 10.1016/j.media.2007.10.009
 23. Kuruvilla S, Janardhanan R, Antkowiak P et al (2015) Increased extracellular volume and altered mechanics are associated with LVH in hypertensive heart disease, not hypertension alone. *JACC Cardiovasc Imaging* 8:172–80. doi: 10.1016/j.jcmg.2014.09.020
 24. Hinojar R, Varma N, Child N et al (2015) T1 Mapping in Discrimination of Hypertrophic Phenotypes: Hypertensive Heart Disease and Hypertrophic Cardiomyopathy: Findings From the International T1 Multicenter Cardiovascular Magnetic Resonance Study. *Circ Cardiovasc Imaging* 8:e003285. doi: 10.1161/CIRCIMAGING.115.003285
 25. Treibel TA, Zemrak F, Sado DM et al (2015) Extracellular volume quantification in isolated hypertension - changes at the detectable limits? *J Cardiovasc Magn Reson* 17:74. doi: 10.1186/s12968-015-0176-3
 26. Rodrigues JCL, Amadu AM, Dastidar AG et al (2016) Comprehensive characterisation of hypertensive heart disease left ventricular phenotypes. *Heart* 102:1671-9. doi: 10.1136/heartjnl-2016-309576
 27. Rodrigues JCL, Amadu AM, Ghosh Dastidar A et al (2017) ECG strain pattern in

- hypertension is associated with myocardial cellular expansion and diffuse interstitial fibrosis: a multi-parametric cardiac magnetic resonance study. *Eur Hear J – Cardiovasc Imaging* 18:441-450. doi: 10.1093/ehjci/jew117
28. Miyoshi H, Oishi Y, Mizuguchi Y et al (2015) Association of left atrial reservoir function with left atrial structural remodeling related to left ventricular dysfunction in asymptomatic patients with hypertension: evaluation by two-dimensional speckle-tracking echocardiography. *Clin Exp Hypertens* 37:155–65. doi: 10.3109/10641963.2014.933962
 29. Matsuyama N, Tsutsumi T, Kubota N et al (2009) Direct action of an angiotensin II receptor blocker on angiotensin II-induced left atrial conduction delay in spontaneously hypertensive rats. *Hypertens Res* 32:721–6. doi: 10.1038/hr.2009.89
 30. Dernellis JM, Vyssoulis GP, Zacharoulis AA, Toutouzas PK (1996) Effects of antihypertensive therapy on left atrial function. *J Hum Hypertens* 10:789–94.
 31. Coelho-Filho OR, Shah R V., Neilan TG et al (2014) Cardiac Magnetic Resonance Assessment of Interstitial Myocardial Fibrosis and Cardiomyocyte Hypertrophy in Hypertensive Mice Treated With Spironolactone. *J Am Heart Assoc* 3:e000790. doi: 10.1161/JAHA.114.000790
 32. Tsang TSM, Barnes ME, Gersh BJ et al (2003) Prediction of risk for first age-related cardiovascular events in an elderly population: the incremental value of echocardiography. *J Am Coll Cardiol* 42:1199–205.
 33. Leung DY, Boyd A, Ng AA et al (2008) Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. *Am Heart J* 156:1056–64. doi:

- 10.1016/j.ahj.2008.07.021
34. Posina K, McLaughlin J, Rhee P et al (2013) Relationship of phasic left atrial volume and emptying function to left ventricular filling pressure: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 15:99. doi: 10.1186/1532-429X-15-99
 35. Russo C, Jin Z, Homma S et al (2012) Left atrial minimum volume and reservoir function as correlates of left ventricular diastolic function: impact of left ventricular systolic function. *Heart* 98:813–20. doi: 10.1136/heartjnl-2011-301388
 36. Gupta S, Matulevicius SA, Ayers CR et al (2013) Left atrial structure and function and clinical outcomes in the general population. *Eur Heart J* 34:278–285. doi: 10.1093/eurheartj/ehs188
 37. Schafer S, Viswanathan S, Widjaja AA et al (2017) IL11 is a crucial determinant of cardiovascular fibrosis. *Nature* nature24676. doi: 10.1038/nature24676
 38. Rogers T, Puntmann VO (2014) T1 mapping - beware regional variations. *Eur Hear J - Cardiovasc Imaging* 15:1302–1302. doi: 10.1093/ehjci/jeu082
 39. Treibel TA, Kozor R, Schofield R et al (2018) Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. *J Am Coll Cardiol* 71:860–871. doi: 10.1016/j.jacc.2017.12.035
 40. Marvao A De, Dawes TJW, Shi W et al (2015) Precursors of Hypertensive Heart Phenotype Develop in Healthy Adults. *JACC Cardiovasc Imaging* 8:1260–9. doi: 10.1016/j.jcmg.2015.08.007
 41. Habibi M, Samiei S, Ambale Venkatesh B et al (2016) Cardiac Magnetic Resonance-Measured Left Atrial Volume and Function and Incident Atrial

Fibrillation: Results From MESA (Multi-Ethnic Study of Atherosclerosis). *Circ Cardiovasc Imaging* 9:e004299. doi: 10.1161/CIRCIMAGING.115.004299

Figure legends

Figure 1: The biplane area-length method to measure LAV. LAVmax was measured at maximal atrial dilatation occurring at LV end-systole just before mitral valve opening, as before. Briefly, the image on **A)** LV long-axis 4-chamber (A1 = atrial area, L1 = atrial length) and **B)** 2-chamber SSFP cines (A2 = atrial area, L2 = atrial length) immediately preceding the opening of the mitral valve was used for analysis of LAVmax. First, LA length was measured from the mitral annular plane to the posterior aspect of the LA wall, parallel to the LV long-axis on both 4-chamber and 2-chamber SSFP cines. The endocardial border of the LA was also manually contoured at LAVmax, excluding the LA appendage and pulmonary venous confluence. RA=right atrium, RV=right ventricle, LV=left ventricle

Figure 2: The phasic volumetric method for assessing left atrial function. A) LAVmin measured at mitral valve closure. B) LAVpre-A measured just prior to left atrial contraction. C) LAVmax measured just before mitral valve opening. RA = right atrium, RV = right ventricle, LV = left ventricle

Figure 3: Study design and exclusions. *Image artifact from implantable loop recorder device precluding volumetric assessment from LV short axis SSFP cine stack.

Figure 4: A & B) The relationship between LV mass and LA volume in 86 hypertensive patients (n=23 with LAE, n=63 without LAE) and 20 controls. **A)** Scatterplot demonstrates positive correlation between indexed LV mass and indexed LAVmax ($R=0.376$, $P<0.0001$). **B)** Scatterplot demonstrates positive correlation between

indexed LV mass and indexed LAVmin ($R=0.616$, $P<0.0001$). **4 C & D**) The relationship between LAVmax and LV fibrosis in 86 hypertensive patients ($n=23$ with LAE, $n=63$ without LAE). **C**) Scatterplot demonstrates positive correlation between ECV and indexed LAVmax ($R=0.359$, $P=0.001$). **D**) Scatterplot demonstrates positive correlation between ECV and indexed LAVmin ($R=0.390$, $P<0.0001$).

Figure 5: Relationship between LA function and LV fibrosis in 86 hypertensive patients ($n=23$ with LAE, $n=63$ without LAE). **A**) Scatterplot demonstrates negative correlation between indexed myocardial interstitial volume and LA total reservoir function ($R=-0.437$, $P<0.0001$). **B**) Scatterplot demonstrates negative correlation between indexed myocardial interstitial volume and LA passive conduit function ($R=-0.316$, $P=0.003$). **C**) There was no significant correlation between indexed interstitial volume and LA contractile pump function ($R=-0.167$, $P=0.125$). **D**) Scatterplot demonstrates negative correlation between indexed myocardial interstitial volume and LA expansion index ($R=-0.377$, $P<0.0001$).

Table 1: Scan parameters for native and post contrast T1-mapping sequences

	Native T1-mapping		Post contrast T1-mapping	
	HR < 90 bpm	HR > 90 bpm	HR < 90 bpm	HR > 90 bpm
TR (ms)	314.85	374.95	394.85	374.95
TE (ms)	1.12	1.00	1.12	1.00
Slice thickness (mm)	8	8	8	8
Voxel size (mm)	2.1 x 1.4 x 8	2.4 x 1.9 x 8	2.1 x 1.4 x 8	2.4 x 1.9 x 8
Matrix	144 x 256	128 x 192	144 x 256	128 x 192
No. acquired heart beats	5	5	4	4
No. recovery heart beats	3	3	1	1

HR = heart rate, bpm = beats per minute, TR = repetition time, TE = echo time, ms = milliseconds, mm = millimetres

Table 2: Demographic and CMR data

		Hypertensive	
	Controls (n=20)	No LAE (n=63)	LAE (n=23)
Age (year)	48 ± 13	48 ± 14	52 ± 14
Gender (% male)	55	60	48
BMI (kg/m²)	28 ± 5	31 ± 6	30 ± 6
Diabetes mellitus (%)	0	13	9
Heart rate (beats/min)	71 ±10	73 ± 13	64 ± 10^^^
Office systolic blood pressure (mmHg)	130 ± 13	166 ± 27 \$\$\$	169 ± 35 ***
Office diastolic blood pressure (mmHg)	80 ± 11	96 ± 12 \$\$\$	97 ± 17 ***
ESH/ESC office BP grade			
- Controlled (%)	...	6	13
- High normal (%)	...	3	4
- Grade 1 (%)	...	30	26
- Grade 2 (%)	...	32	13
- Grade 3 (%)	...	27	39
- Isolated systolic (%)	...	3	4
No. antihypertensive medications (n)	0	2 ± 2	3 ± 2 ***
ACEi/ARB (%)	0	76	83 ***

One-way ANOVA with Bonferonni post-hoc correction or Chi squared test as appropriate:

Controls vs LAE: *** p < 0.001

Controls vs No LAE : \$\$\$ p < 0.001

LAE vs No LAE: ^^^ p < 0.001, LAE vs No LAE

Table 3: Demographic and CMR data

		Hypertensive	
	Controls (n=20)	No LAE (n=63)	LAE (n=23)
LV data			
EF (%)	66 ± 8	68 ± 8	64 ± 11
Indexed EDV (ml/m ²)	70 ± 12	73 ± 16	89 ± 17 *** ^^^
Indexed ESV (ml/m ²)	24 ± 7	24 ± 10	34 ± 17 * ^^^
Indexed SV (ml/m ²)	46 ± 9	49 ± 10	56 ± 10 ** ^
Cardiac output (l/min ¹)	6.3 ± 1.4	6.6 ± 3.0	6.7 ± 2.1
Mass : volume (g/ml)	0.82 ± 0.13	1.16 ± 0.30 \$\$\$	1.12 ± 0.41 **
Indexed LV mass (g/m ²)	56 ± 8	84 ± 22 \$\$\$	97 ± 33 *** ^
LV strain data			
Peak circumferential strain (%)	-17.6 ± 2.7	-16.8 ± 3.2	-15.7 ± 4.2
Peak circumferential systolic strain rate (%/sec)	-102.7 ± 13.4	-108.7 ± 29.7	-86.4 ± 24.8 ^^
Peak circumferential diastolic strain rate (%/sec)	102.3 ± 26.9	94.5 ± 24.9	83.3 ± 31.9

Continued...

Table 3: Demographic and CMR data continued

		Hypertensive	
	Controls (n=20)	No LAE (n=63)	LAE (n=23)
LV T1 mapping data			
Native T1 (ms)	1030 ± 42	1039 ± 36	1044 ± 52
ECV (%)	...	27 ± 3	30 ± 4 ^^
Indexed interstitial volume (ml/m²)	...	21 ± 7	28 ± 12 ^
Indexed myocardial cell volume (ml/m²)	...	57 ± 15	64 ± 21
LA data			
Indexed LAVmax (ml/m²)	38 ± 8	42 ± 8	65 ± 8 ***
Indexed LAVmin (ml/m²)	16 ± 3	20 ± 6 §	34 ± 10 ***
Reservoir function (%)	57 ± 9	51 ± 9 §	47 ± 11 **
Conduit function (%)	35 ± 10	28 ± 12	26 ± 9 *
Pump function (%)	33 ± 9	31 ± 13	30 ± 11
Expansion index (%)	133 ± 31	114 ± 38	96 ± 37 **

One-way ANOVA with Bonferonni post-hoc correction:

Controls vs LAE:	* p < 0.05, Controls vs LAE	** p < 0.01, Controls vs LAE	*** p < 0.001, Controls vs LAE
Controls vs No LAE:	§ p < 0.05, Controls vs No LAE	§§ p < 0.01, Controls vs No LAE	§§§ p < 0.001, Controls vs No LAE
LAE vs No LAE:	^ p < 0.05 LAE vs No LAE	^^ p < 0.01, LAE vs No LAE	^^^ p < 0.001, LAE vs No LAE

Table 4: CMR data corrected for covariates[¶]

		Hypertensive	
	Controls (n=20)	No LAE (n=63)	LAE (n=23)
LV data			
EF (%)	65 ± 2	68 ± 1	64 ± 2
Indexed EDV (ml/m ²)	74 ± 2	72 ± 16	89 ± 3 * ^^^
Indexed ESV (ml/m ²)	28 ± 3	24 ± 2	33 ± 2 ^^
Indexed SV (ml/m ²)	47 ± 3	49 ± 1	56 ± 2 * ^
Cardiac output (l/min ¹)	6.9 ± 0.8	6.4 ± 0.3	6.7 ± 0.6
Mass : volume (g/ml)	0.94 ± 0.09	1.12 ± 0.04	1.12 ± 0.06
Indexed LV mass (g/m ²)	72 ± 6	79 ± 2	95 ± 4 ** ^^
LV strain data			
Peak circumferential strain (%)	-15.8 ± 0.8	-17.3 ± 0.4	-15.9 ± 0.6
Peak circumferential systolic strain rate (%/sec)	-89.5 ± 6.6	-111.2 ± 3.3 §	-90.0 ± 7.4 ^^
Peak circumferential diastolic strain rate (%/sec)	89.5 ± 6.6	97.6 ± 2.9	86.2 ± 4.8

Continued...

Table 4: CMR data corrected for covariates[¶] continued

		Hypertensive	
	Controls (n=20)	No LAE (n=63)	LAE (n=23)
LV T1 mapping data			
Native T1 (ms)	1047 ± 12	1036 ± 5	1042 ± 9
ECV (%)	...	27 ± 4	30 ± 6 ^^^
Indexed interstitial volume (ml/m²)	...	21 ± 1	29 ± 2 ^^^
Indexed myocardial cell volume (ml/m²)	...	57 ± 2	65 ± 3 ^
LA data			
Indexed LAVmax (ml/m²)	40 ± 2	42 ± 1	64 ± 2 *** ^^^
Indexed LAVmin (ml/m²)	19 ± 2	20 ± 1	34 ± 1 *** ^^^
Reservoir function (%)	53 ± 3	52 ± 1	48 ± 2
Conduit function (%)	32 ± 3	29 ± 1	26 ± 2
Pump function (%)	30 ± 3	32 ± 1	30 ± 2
Expansion index (%)	124 ± 11	115 ± 5	103 ± 7

[¶]General linear models accounting for the covariates of age, gender, BMI, diabetes, office SBP and DBP and number of anti-hypertensive medications. Data are presented as mean ± standard error.

One-way ANOVA with Bonferonni post-hoc correction:

Controls vs LAE:	* p < 0.05, Controls vs LAE	** p < 0.01, Controls vs LAE	*** p < 0.001, Controls vs LAE
Controls vs No LAE:	§ p < 0.05, Controls vs No LAE	§§ p < 0.01, Controls vs No LAE	§§§ p < 0.001, Controls vs No LAE
LAE vs No LAE:	^ p < 0.05 LAE vs No LAE	^^ p < 0.01, LAE vs No LAE	^^^ p < 0.001, LAE vs No LAE

Table 5: Determinants of LAE

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1.02 [0.98–1.05]	=0.309
Male gender	1.66 [0.63–4.34]	=0.302
BMI (kg/m ²)	0.97 [0.88–1.05]	=0.427
Office SBP (mmHg)	1.00 [0.99–1.02]	=0.688
Office DBP (mmHg)	1.01 [0.97–1.04]	=0.784
Diabetes mellitus	1.53 [0.30–7.79]	=0.610
Indexed LV mass (g/m ²)	1.02 [1.00–1.04]	=0.034*	1.00 [0.98–1.02]	=0.938
ECV (%)	1.30 [1.10–1.54]	=0.002*	1.24 [1.04–1.48]	=0.017*
Peak circ systolic strain rate (%/sec)	1.04 [1.01–1.07]	=0.003*	1.04 [1.01–1.07]	=0.022*

OR=odds ratio, CI=confidence interval, * P<0.05